POSITIONING THE INTERNATIONAL SPACE STATION FOR THE UTILIZATION ERA*

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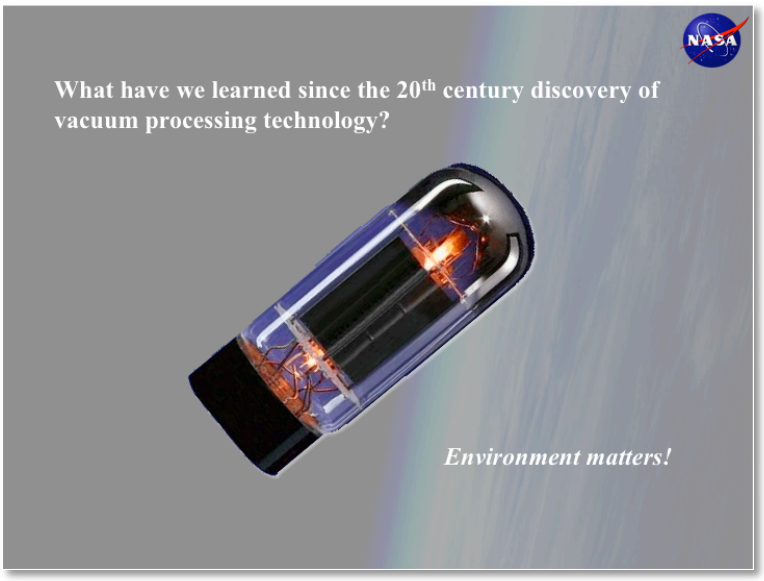
Abstract

The completed International Space Station (ISS) is among the greatest of international cooperative endeavors in the history of science and technology. While the design, assembly and operations to date are remarkable human achievements in their own right, the opening of the utilization era over the next decade presents unprecedented opportunities for advancing research and development of space resources. NASA has been working with international partners in Canada, Europe, Japan and Russia, as well as the U.S. White House and Congress to maximize the value of this extraordinary global asset. Scientific, technological and industrial uses are being enabled through new initiatives that are designed to contribute to both the future of space exploration and the missions of organizations other than space agencies in the domains of public health, energy, the environment and education. International humanitarian projects are on the drawing boards, as is a U.S. independent non-profit foundation for the advancement of scientific research into the realm of applied products and services. During the next 12-18 months, the ISS will be strategically positioned to best support success in these initiatives and unequivocally demonstrate the benefits of international cooperation for peaceful purposes and value-added applications. A new global economy in space is approaching the tipping point.



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Introduction

Attention is turning rapidly to scaling up practical uses of the ISS as completion of the assembly phase draws near. While much has been learned technologically, operationally and scientifically during the planning, development and construction phases, the dawning of full-scale utilization will re-boot the spacecraft for the purposes for which it was originally designed – scientific research, applications development, technological demonstration and industrial growth.

Federal policies have been promulgated through White House direction and Congressional statute[1], in order to ensure research and development (R&D) opportunities are inclusive of both NASA and national mission objectives. Independent review by a Presidential Commission was completed in 2009 under the leadership of seasoned leaders in science, technology and diplomatic affairs.[2] Fiscal resources have been authorized through USG Fiscal Year 2013 with direction to extend the Program through 2020 or beyond. Canada, Europe, Japan and Russia are unanimously "***go.***"

Completing the ISS as originally envisioned and then operating it as a permanently crewed laboratory, observatory and test bed has been an enduring controversy. The high cost (~ $60 billion according to mandated auditing standards) and long schedule (~ 25 years since the conceptual design phase was initiated) has nonetheless yielded an international asset with extraordinary technical performance capabilities. Expectations for productivity likewise run high for the next decade. As the systems integration and management leader for the ISS Program, NASA will ultimately be accountable for the outcome on the behalf of all international partners. In the U.S., future policy decisions regarding whether to decrease, sustain, or increase fiscal appropriations to human space flight will be strongly influenced by ISS productivity.

Two principle factors will determine ISS productivity in the coming years. Can ISS-based R&D truly have a substantive impact on future paths in science and technology? There are both cynics and visionaries on this question, which is to be expected in any emerging field of research. Also, will the programmatic opportunities and constraints allow for the R&D potential to actually be realized in practice? History is abounding with lost opportunities, sometimes even signaling the decline of entire societies when viewed retrospectively.

The following discussion will review both the R&D and programmatic prospects in the light of current scientific, technical and political conditions. After 25 years of due diligence by NASA on the subject matter, the decision to "use or lose" the ISS opportunity is now up to the governments of the respective international partners. As has been the history of human space flight, U.S. leadership may well determine the final outcome.

Research and Development Prospects

Beneficial uses of space were first considered while drawing up the seminal legislation that formed NASA in 1958. The National Aeronautics and Space Act recognized the need for ***"…studies of the potential benefits to be gained from, the opportunities for, and the problems involved in the utilization of space activities for peaceful and scientific purposes."*** The NASA programs that followed over the next 25 years (1959-1984) were largely devoted to establishing footholds in low-Earth orbit and on the lunar surface, so that humans could learn to live and work productively in extreme space environments. Mercury, Gemini, Apollo and Skylab brought progressively increasing laboratory research components that revealed new biological and physical phenomena unique to the "free fall" environment of orbital spacecraft. Then, in 1981, the era of the Space Shuttle began and with it came opportunities to deploy the first fully outfitted laboratories for "bench top" experimentation in the new field of microgravity science and applications. Spacelab flights enabled by European and Japanese participation, and later U.S. commercial Spacehab flights, resulted in 5-7 days per mission of dedicated laboratory-based experimentation across a virtually unlimited spectrum of scientific fields.

It would be accurate to characterize these last 25 years (1985-2010) of Space Shuttle based-research as a highly effective *survey phase*. During this period, 15 Spacelab and 8 Spacehab

[1] President's FY-2011 Budget, submitted to the U.S. Congress Feb, 1, 2010 and NASA Authorization Act of 2010, Section 504 Management of the ISS National Laboratory, enacted Oct 11, 2010.
[2] Review of U.S. Human Space Flight Plans Committee, *Seeking a Human Spaceflight Program Worthy of a Great Nation*, Oct. 2009.

pressurized laboratory module missions were flown for a total of approximately 120 days in the microgravity environment. In addition, the Shuttle-Mir program and ISS assembly phase allowed limited opportunities to conduct research on the margins of higher priority spacecraft operations. However, in sum total, less than one year of dedicated laboratory research time accrued over those 25 years. Nonetheless, this period yielded provocative research findings that provide a reliable indicator of the prospects for future research payoffs during the ISS utilization era.

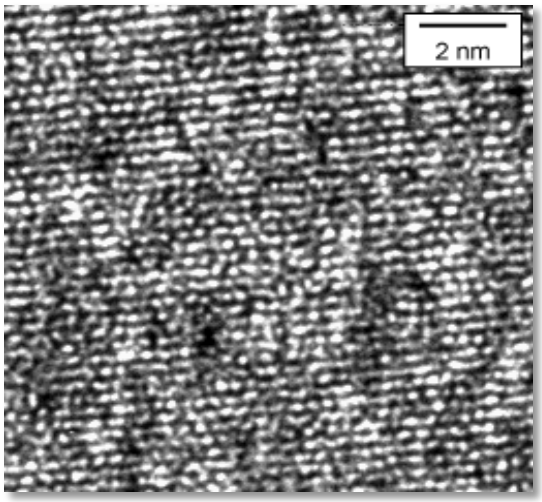


Figure 1: High resolution TEM image of a crystalline zirconium alloy. The bright spots are long rows of atoms, viewed end-on. Notice how these spots are very regularly arranged, proving that this material has a crystalline structure.

Now, it's time to conclude the broad survey phase and focus on the most promising opportunities. While basic research must always continue, the research portfolio must also increase emphasis on applications-driven objectives based on the prior knowledge acquired. Success in achieving these new applications objectives will most effectively compel further growth in the national R&D investment for microgravity science and applications for the future.

Before reviewing these prospects, it is important to also acknowledge that the lag period from basic discovery to product availability is not short. The notion that a single experimental finding is going to yield a profound discovery that rapidly impacts society in the form of widely available products is well beyond the bounds of history. Albert Einstein first proposed his theory of mass-energy equivalence, $E=mc^2$, in 1905, yet it took another 40 years before the principle was successfully demonstrated through a nuclear fission reaction. This classic "40 year lag time" between discovery and application is often cited, though obviously not an absolute condition.

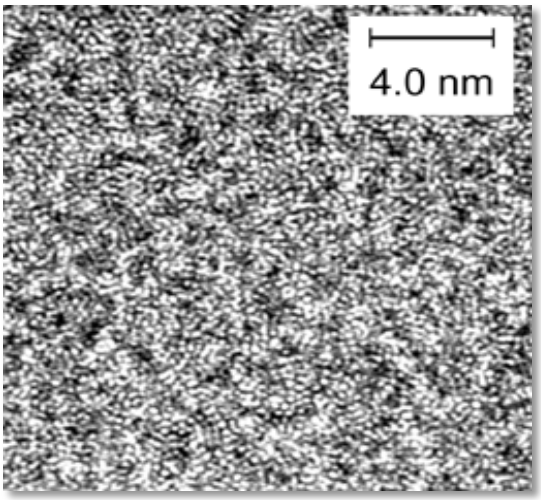


Figure 2: High resolution TEM image of an amorphous zirconium alloy. In contrast to Figure 1, the spots are randomly arranged, which tells us that this material is noncrystalline.

The National Science Foundation sponsored the landmark "TRACES"[3] study in an attempt to better understand the time-scales associated with discovery and application (Illinois Institute of Technology Research, 1968). This work was followed by TRACES-II and –III conducted by Battelle-Columbus Laboratories in 1973 and 1976. The results of these retrospective tracer studies are summarized as having found ***"…that a lengthy period, often about twenty years, occurs between an invention in basic research and its application in weaponry or medical innovation."***[4]

With these considerations in the forefront, we are now prepared to turn to several of the more provocative findings over the 25-year survey phase in microgravity science and applications.

Thermo-physical Properties Measurement

Under microgravity conditions, electromagnetic levitators can be employed to position and manipulate samples in free space without the contaminating effects of a container wall. In addition, the sample can be transitioned from solid to liquid phases by a flux of energy into the processing region of the chamber. In this form of

[3] Technology in Retrospect and Critical Events in Science
[4] Rogers, E., Diffusion of Innovations, 5th Edition, Free Press, pp. 176-177, 2003.

container-less processing, the sample avoids surface contamination effects, such as nucleation, that can confound thermo-physical properties measurement under 1G conditions. The capability to understand the thermodynamics of materials and alloys undergoing changes of state, in order to improve material performance and achieve new compounds that can be produced on the ground, has long been hypothesized as a useful benefit of space laboratories.

Metallic glasses (aka amorphous metals) represent a class of materials that have been sought after because they could lend themselves to thermoplastic forming while softened at elevated temperature, and yet still retain their amorphous structure to yield improved properties. Figures 1 and 2 are high-resolution transmission electron microscope images of zirconium alloy in the conventional crystalline and amorphous, or metallic glass, state.[5]

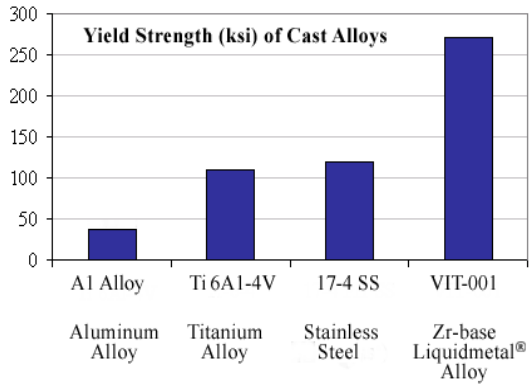


Figure 3: Comparative yield strength (ksi) of cast alloys with Zr-base Liquidmetal® alloy.

In 1997, the Microgravity Sciences Lab-1 mission was flown on the Shuttle Columbia and experiments were conducted in an electromagnetic container-less processing facility (TEMPUS[6]). This research yielded the first measurements of specific heat and thermal expansion of glass-forming metallic alloys, as well as the highest temperature (a maximum of 2,000 ºC) and largest undercooling (to 340 ºC) ever achieved in space (Glade, 2000). Alternating current modulation calorimetry was employed to measure the specific heat capacity of the undercooled and equilibrium liquid, and a differential thermal analyzer obtained the heats of fusion, and solidus and liquidus temperatures of the alloys of interest. As a result of these experiments, the thermodynamic properties of the alloys were obtained and the capability to produce bulk metallic glasses on the ground was advanced. The performance in terms of yield strength and elastic limit for one new material, zirconium based Liquidmetal®, is provided in Figures 3 and 4.

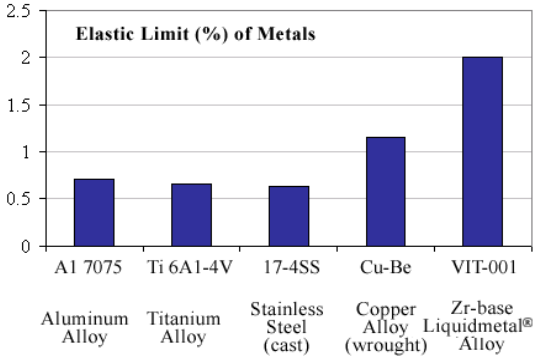


Figure 4: Comparative elastic limit (%) of metals with Zr-base Liquidmetal® alloy.

Liquidmetal Technologies (LQMT) was incorporated in 1987 in the State of California and became a Delaware Corporation in May 2003. LQMT's initial public offering was conducted in May 2002, and common stock began trading on the NASDAQ under the symbol LQMT.[7] On August 5, 2010, LQMT entered into a Master Transaction Agreement with Apple Inc. pursuant to which (i) LQMT contributed substantially all of its intellectual property assets to a newly organized special-purpose, wholly-owned subsidiary (the "IP Company"), (ii) the IP Company granted to Apple a perpetual, worldwide, fully-paid, exclusive license to commercialize such intellectual property in the field of consumer electronic products in exchange for a license fee, and (iii) the IP Company granted back to Liquidmetal a perpetual, worldwide, fully-paid, exclusive license to commercialize such intellectual property in all other fields of use.[8]

Materials science experts have characterized metallic glasses as the 3rd generation in a materials revolution that began with steel and was followed by plastics.

Cellular Tissue Culturing

Under microgravity conditions, a rotating wall bioreactor allows cells to grow and propagate in

[5] Hufnagel, T., 2007, Johns Hopkins University.
[6] Tiegelfreis Elektromagnetisches Prozessieren Unter Schwerelosigkeit

[7] http://www.liquidmetal.com/index/
[8] Information contained in LQMT's 8K filing with Securities and Exchange Commission, August 9, 2010.

a three-dimensional matrix similar in process to cell growth in the human body. This is not unexpected, because cells in the human body essentially live suspended in the intercellular media at the micro-level, and are effectively insulated from the 1G force field that we experience as whole organisms at the macro level.

However, this did pose a significant problem in biomedical research, since conventional cell culturing in a ground-based laboratory typically took place on a flat surface and was thus limited to two dimensions. While cells could indeed grow and propagate in 2D, they did not fully reflect the 3D conditions in human physiology – the cells that differentiate tissue into specific functions lacked the environmental cues that signal the process to begin.

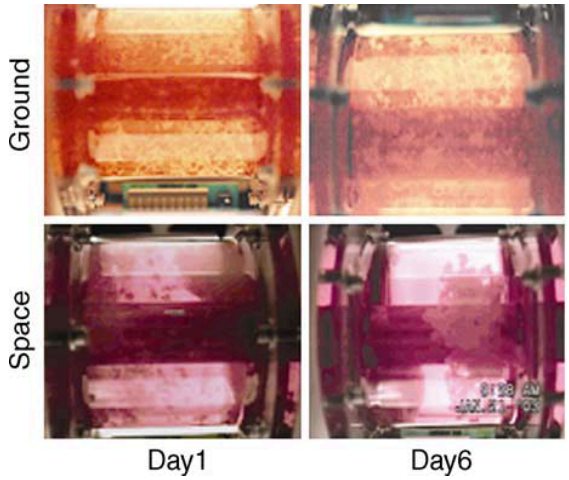
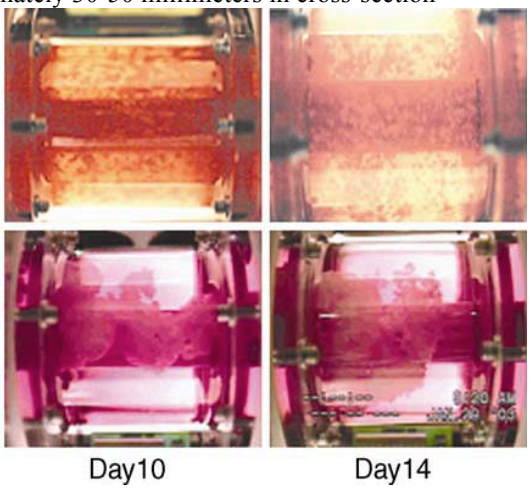


Figure 5: Formation of large prostate cancer organoids with the 3D rotating wall vessel bioreactor in space. Much larger prostate organoids were formed in space (30-50 cm across) as compared to the parallel ground study (3-5 cm) despite no difference in glucose utilization rate between ground and space studies.

In the late 1980's, NASA scientists began experiments on the effect of cell culturing under neutral-buoyancy suspension conditions on the ground with an eye toward later improving the technique in space through microgravity processing. As a result of this work, the bioreactor was developed and this new technology rapidly transitioned into broad use by biomedical researchers at large. Today, suspension 3D cell culturing is a valuable tool in the ground-based study of infectious disease mechanisms (Barrila, 2010). However, bioreactor experiments performed in the 1990's during the Shuttle-Mir Program, and later on Shuttle Spacehab missions, also confirmed that the microgravity environment of space yielded even better results as was originally postulated.

In order to study cancer tumor growth, individual cancer cells must be aligned and organized in 3D in a manner similar to that experienced in the human body. In the case of prostate cancer, the proximity of epithelial cells to stroma cells in the 3D matrix has a direct effect on metastasis that cannot be observed when using a 2D growth technique. This was tested in the bioreactor on Shuttle Columbia mission STS-107 in 2003 and the results were remarkable. Cancer cells were cultured with host bone stroma cells on the ground in a suspension bioreactor under identical conditions to a bioreactor in space operating under microgravity conditions. The microgravity conditions allowed tumor growth up to approximately 30-50 millimeters in cross-section



compared to approximately 3-5 millimeters under suspension on the ground (Wang, 2005). Figure 5 provides the actual pictures transmitted from space during the 14-day culturing period.

In 2002, the privately held company Regenetech, Inc. was formed in Houston, TX and entered into a Sponsored Research Agreement with M.D. Anderson Cancer Center. Shortly thereafter, Regenetech licensed its first intellectual property for treatment of sickle cell anemia and began expanding research into adult stem cells. By 2009, they had achieved a 100-fold expansion in the safe production of mesenchymal adult stem cells and entered into a license agreement with the Hospital Corporation of America of Nashville, TN.[9]

[9] http://www.regenetech.com/

The bioreactor was a major technological innovation in ground-based research – three-dimensional tissue culturing in space allows conditions matching cell growth in humans that have never before been available.

Macromolecular Crystallization

Under microgravity conditions, large and complex biological macromolecules (e.g., proteins, nucleic acids, polysaccharides…) have been proven to grow larger and more perfectly than on the ground in many instances. The absence of thermal convection, sedimentation, buoyancy, hydrostatic pressure, and gradients inherent in natural 1G phenomena all contribute to improved growth under microgravity conditions. With the advent of large-scale particle accelerators for x-ray and neutron diffraction, this allows the precise determination of molecular structures needed for therapeutic drug design.

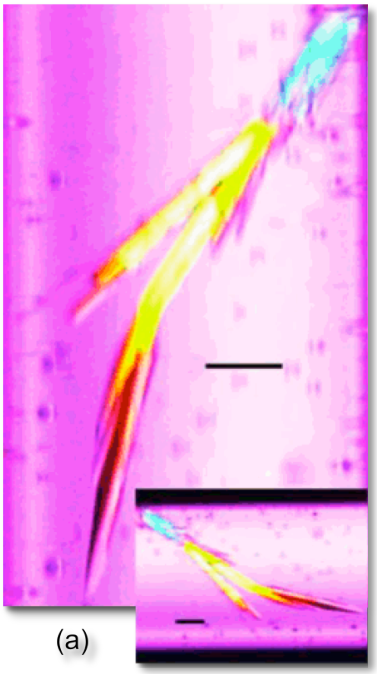
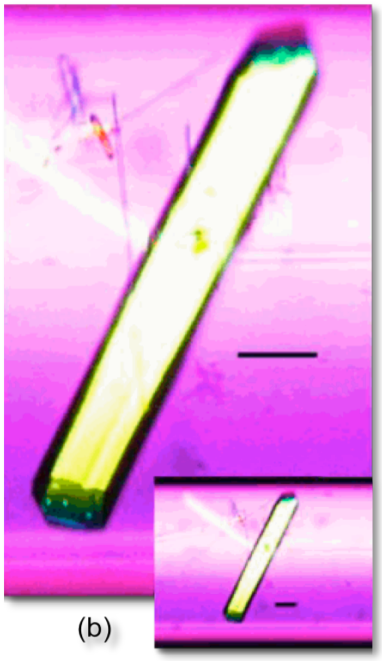


Figure 6: Crystals of H-PGDS grown under terrestrial (a) and microgravity (b) conditions. In the microgravity experiment plate-like crystals were grown with good morphology. Scale bar corresponds to 100 µm.

Scientists at NASA began working with academic and industrial investigators in the mid-1980's to develop spaceflight systems that employed a variety of macromolecular crystallization techniques. While success came quickly for a limited number of samples, it also became evident that longer microgravity exposure times (i.e., 30-90 days) would be needed to achieve a high reliability rate. This was recognized by Nobel laureate Herbert A. Hauptman, PhD in 1995 when he wrote to the U.S. Congress, ***"It is clear that with the additional capabilities that the Space Station will offer, this type of research will progress at a much more rapid rate."***[10] The availability of the ISS notwithstanding, by 2002 over twenty articles in peer-reviewed journals attested to the improved diffraction-quality, low-mosaicity crystals being obtained under microgravity conditions, and the clear contribution to drug design efforts.[11]



Working with the Japan Aerospace Exploration Agency and the Federal Space Agency of Russia, Dr. Yoshihiro Urade of the Osaka Bioscience Institute undertook efforts to grow human hematopoietic prostaglandin D synthase (HPGDS) on the Russian segment of the ISS in 2007. HPGDS is an enzyme whose synthesis relates to causation in Duchenne muscular dystrophy (DMD). High quality crystals that diffracted from 1.0-1.5 Å resolution were obtained under microgravity conditions. The space-grown crystals were also of low mosaicity (0.54-0.62º) in comparison to their counterparts (0.81-3.39º) grown under 1G (Takahashi, 2010). Mosaicity is an important

[10] Letter from Herbert A. Hauptman, PhD to Honorable David Minge, U.S. House of Representatives, June 23, 1995.
[11] DeLucas, L., (ed) *"New and Enabling Information from Microgravity-Grown Protein Crystals"*, unpublished, Attachment 1 to Memorandum from Director, NASA Research Integration Division to Chair, Research Maximization and Prioritization Task Force, May 2, 2002.

measure of the quality of the crystal for diffraction analysis. Figure 6 provides a visual comparison of the differences in quality despite similarities in physical size.

Based on the molecular structure information obtained from the space-grown HPGDS crystals, Dr. Urade's research team designed an inhibitor drug and administered it to one of two canines suffering from DMD. The progression of DMD in the treated canine dramatically slowed within eleven months. These results were revealed in public at the 2010 International Astronautics Congress in Prague, Czechoslovakia, where Dr. Urade encouraged hope for people around the world who suffer the debilitating effects of muscular dystrophy.[12]

Gaining insight into the molecular structure of causative biochemical agents is the first step in the design of drugs to interdict many chronic human diseases.

Differential Gene Expression

Under microgravity conditions, gene expression exhibits radical changes. In the late 1990s, scientists at Tulane University working under a NASA grant hypothesized that the culture of cells under microgravity conditions could yield the optimum environment for elucidating the dynamics of cell differentiation. They suggested that there are three needed physical conditions that can only be achieved by a bioreactor operating in space: three dimensionality, low shear and turbulence, and co-spatial relation of dissimilar cell types (Hammond, 2000).

On the Space Shuttle STS-90 *Neurolab* mission in 1998, human renal cortical cells were successfully cultured in the NASA bioreactor and displayed an unequivocal change in gene expression. Figure 7 summarizes the magnitude of change by comparing two cases: microgravity and ground-based suspension. These results led the research team to conclude, ***"Studies of tissue-specific differentiation on the Space Station laboratory will act as a factory for state-of-the-art molecular analysis on mechanisms of gene expression in optimized suspension culture experiments"*** (Hammond, 2001).

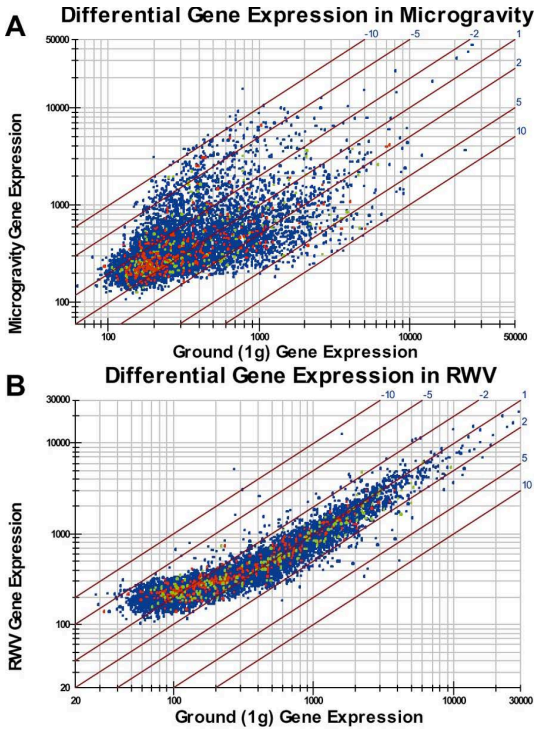


Figure 7: Gene array. Each cell culture condition including microgravity (A) and terrestrial rotating wall vessel (B) is compared with a static nonadherent bag culture. In each panel, 10,000 individual genes are represented by individual dots. Sheer stress proteins and heat shock proteins are shown in green, and transcription factors are in red. Gene expression is displayed on a log scale to base 10. Changes greater than threefold are outside the region of background noise. For each gene, the distance from the origin denotes level of gene expression, and movement on the x- and y-axes reports changes in gene expression compared with static bag control culture. More than 1,600 (1,632) change more than the specific threshold of threefold up and down in the flight (microgravity) culture (A) and more than 900 genes (914) changed in the terrestrial RWV culture (B); only a few genes (5) changed in a terrestrial centrifuge culture (not shown).

Further advances over the past decade in analytical instruments and techniques for molecular biology are now revealing that the root causes of many biochemical reactions are physical forces acting at the cellular level.[13] These stimuli, or lack thereof, signal specific genes to up- or down-regulate in response, and represent the starting point of complex suites of biochemical reactions along signal transduction pathways that contemporary scientists are carefully deciphering. The availability of an ISS-based bioreactor would allow the development of highly advanced cell culture models that are easily refined based on microgravity results to produce a new wealth

[12] http://www.youtube.com/watch?v=0fwr-FR18ms&feature=channel (see minutes 20:21 – 34:35).

[13] Akst, J., *Full Speed Ahead: Physical forces acting in and around cells are fast—and making waves in the world of molecular biology*, The Scientist, Vol.23, Issue 12, p.26, 2009.

of knowledge in signal transduction and metabolic pathways associated with human disease.

Gene expression regulates physiological performance and is pivotal to the healthy maintenance of all human systems.

Microbial Pathogenicity

Under microgravity conditions, bacterial microbes have been observed to be more virulent than on the ground. During ground-based research using suspension cell culturing techniques, it was found that many changes begin taking place as the gravitational environment is altered from 1G to neutral buoyancy. The bacterial pathogen Salmonella enterica exhibited increased virulence, increased resistance to environmental stresses, and greater survival in macrophages, as well as changes in gene expression (Wilson, 2007). This led the research team to hypothesize that phenotypic and genotypic responses could be further altered under actual microgravity conditions. On Shuttle *Atlantis* mission STS-115 in 2006, the first results were obtained that proved out changes in gene expression and virulence when salmonella cells were cultured in microgravity. This demonstrated the principle that signal transduction pathways at the cellular level are indeed altered in the absence of gravity-induced forces. The finding opened a new window into the understanding of microbial response mechanisms and the processes associated with infectious disease. The experiments also revealed the formation of an extracellular matrix related to the activation of genes that induce formation of biofilms (Figure 8). Since such biofilms can increase the survivability of bacteria, it was also reasonable to conclude that this phenotypic change relates to the increased virulence.

As can be the case, scientific findings obtained under government-funded grants can stimulate private R&D investments. It was in this context that Astrogenetix, Inc. was formed as a subsidiary of Astrotech International. The R&D mission of Astrogenetix is to discover therapeutically relevant and commercially viable biomarkers — substances used as indicators of biologic states — in the microgravity environment of space.[14] Scientists at Astrogenetix reasoned that specific genes might be regulating the increased virulence in salmonella, and this information could potentially be used to develop a vaccine. They also developed an in-space assay method that allowed research with genetically altered bacteria to identify strains that could be effective as vaccines.[15] This experimental model has since identified gene deletions for both Salmonella and Methicillin resistant staphylococcus aureus (MRSA) for further maturation in vaccine based applications.

Bacterial pathogens are a significant contributor to infectious disease and the opportunity is emerging for effective management through microgravity-based protocols for therapeutic drug development.

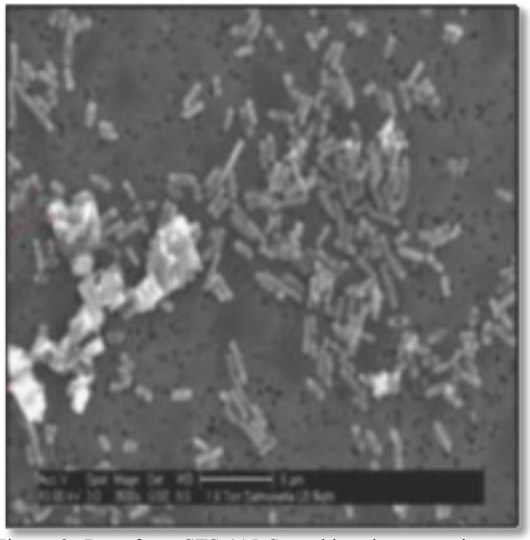


Figure 8: Data from STS-115 S. typhimurium experiments. SEM of spaceflight bacteria showing (white areas) the formation of an extracellular matrix and associated cellular aggregation of space flight cells. (Magnification: X3.500.)

The examples reviewed above demonstrate just a few promising R&D prospects for the future. There is no shortage of high-quality anecdotal evidence that microgravity conditions can reveal important information about the nature of biological and physical systems. What remains necessary is consistent access to ISS laboratories, in order to sustain focused R&D projects and obtain reproducible results that are compelling to the mainstream science community. These "proof-of-concept" demonstrations are also needed to transition from the public to private funding stage in the coming decade.

[14] http://www.astrogenetix.com/

[15] From Statement of Jeanne L. Becker, PhD Before the Subcommittee on Science and Space, Committee on Commerce, Science and Transportation, U.S. Senate, October 21, 2009.

If one accepts that the R&D prospects are clear, then the challenge turns to the programmatic prospects. Consistent space transportation, access to ISS resources and accommodations, and funding for applications research become the three key prerequisites to ISS productivity.

Programmatic Prospects

The ***space transportation*** forecast for cargo services to and from the ISS in the coming decade is based on a "global mixed fleet" strategy that has become possible for the first time in the history of human space flight. The Russian *Progress* is a well-proven spacecraft that has been undergoing modernization upgrades for several years. The European Automated Transfer Vehicle (ATV) and Japanese H-II Transfer Vehicle (HTV) are new cargo resupply ships that have both demonstrated the capability to rendezvous with the ISS. Finally, the SpaceX *Falcon 9/Dragon* and Orbital Sciences *Taurus-II/Cygnus* are both scheduled for demonstration in the imminent future, and under NASA contract to begin cargo services to and from the ISS within the next 12-24 months.

In short, the future prospects for space transportation are good provided the ISS partners uphold their commitments. In the case of the U.S., success by Space X and Orbital Sciences in fielding new vehicles on a timely basis will be absolutely critical to ISS productivity.

The ***resources and accommodations*** outlook could hardly be better. The ISS has met all performance requirements set out at the 1993 critical design review and is the most capable multimission spacecraft ever deployed in terms of available experiment sites. These capabilities include >80 sites capable of accommodating 100-300 payloads; power/thermal at 3-6 kWp; crew support of 2000-3000 hrs/yr; and, data telemetry via 300 Mbps downlink, with distributed vacuum, waste gas venting, caution and warning, and fire suppression utilities. This magnitude of resources and accommodations would correspond to roughly 150 prior generation Spacelab missions per year. It has been estimated through regressive linear programming techniques, and validated by manpower-intensive time-lining analyses, that ~ 30% of the connected experiment load could be operated at any given time.[16] This is a similar level as can be expected in typical ground-based laboratories and thus represents a new plateau of capability in space-based R&D.

The NASA funding available for continued basic and ***applications-targeted research*** to demonstrate proofs-of-concept at repeatable levels by independent parties is at a turning point. While the U.S. President's FY-2011 budget proposed only $50 million per year, as compared to ~ $800 million per year at peak funding levels in prior periods, the proposal also includes provisions for a modest $15 million annual investment in a competitively acquired cooperative agreement with a non-profit organization. The purpose of this agreement will be to stimulate, develop and manage uses of the U.S. share of the ISS by organizations other than NASA. In combination with the standing Memoranda of Understanding with other U.S. government agencies and Space Act Agreements with U.S. private firms and universities,[17] there is little doubt remaining that interest levels are increasing as the ISS assembly phase draws to a close.

Conclusion

Completion of the ISS assembly phase fundamentally changes the balance of competing interests, and tips the scale distinctly in favor of deriving tangible benefits from the international investment in ISS to date. The prospects for highly productive applied research are encouraging based on the survey results from the past 25 years of virtually unfettered research. The programmatic elements necessary to success could still fall into place on schedule, but risk remains in terms of demonstrating transportation systems, appropriating and leveraging research funds, and restructuring R&D management mechanisms. The ISS is carefully and deliberately being repositioned in a manner that will ensure this U.S. asset will provide maximum value to the Nation.

The ISS physical and functional capabilities available for R&D and the extraordinarily unique phenomenological nature of the microgravity environment combine to make the ISS a potentially powerful disruptive technology. The opportunity to reach the proverbial tipping point for discov-

[16] Uhran, M.L and Sullivan, J., *An Integration Strategy for Worldwide Research Operations on the International Space Station*, American Institute of Aeronautics and Astronautics, 1996.

[17] For copies of all ISS MOUs and SAAs go to: http://www.nasa.gov/mission_pages/station/research/nlab/index.html

ery-driven research and a new space-based economy is coming within grasp.

Acknowledgments
The results discussed in this paper could not have been obtained without the prior 25-year survey phase in microgravity science that has taken place on the Space Shuttle, Mir Station and International Space Station. Literally hundreds of U.S principal investigators, perhaps a few thousand in the worldwide community, participated in bench top biology, chemistry and physics experimentation. Their hypotheses that a profound change in environmental conditions could yield equally profound insights into nature are the stuff from which futures are made.

Bibliography

1. Barilla, J., et al., (2010) Organotypic 3D cell culture models: using the rotating wall vessel to study host-pathogen interactions. Nature Rev. Micro. 8, 791-801.

2. Glade, S.C., et.al., (2000) Thermodynamics of $Cu_{47}Ti_{34}Zr_{11}Ni_8$, $Zr_{52.5}Cu_{17.9}Ni_{14.6}Al_{10}Ti_5$ and $Zr_{57}Cu_{15.4}Ni_{12.6}Al_{10}Nb_5$ bulk metallic glass forming alloys. J Appl Physics 87:7242-7248.

3. Hammond, T.G., et.al., (2001) Invited Review: Optimized suspension culture: the rotating wall vessel. Am J. Physiol.Renal Physiol 281:F12-F25, 2001.

4. Hammond, T.G., et.al., (2000) Mechanical culture conditions effect gene expression: gravity-induced changes on the space shuttle. Physiol. Genomics 3:163-173.

5. Takahashi, S., et.al., (2010) High-quality crystals of human haematopoietic prostaglandin D synthase with novel inhibitors. Acta Crystallographica F66:846-850.

6. Wang, R., et.al., (2005) Three-dimensional co-culture models to study prostate cancer growth, progression, and metastasis to bone. Seminars in Cancer Biology 15:353-364.

7. Wilson, J.W., et.al., (2007) Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq. PNAS104:16299-16304